Telefax

Ms. Kimberly Littleton Topper
FDA/CDER
Telephone # 301 827-7001
Telefax # 301 827-6801

Re: Questions for the Advisory Committee Meeting
On Orally Inhaled and Nasal Drug Products Subcommittee for
Pharmaceutical Sciences -April 26, 2000

Dear Ms. Topper,

In accordance with the Notice on the Federal Register, Vol. 65, No. 56, Wednesday, March 22, 2000, attached are questions on pending issues we would like submitted to the Advisory Committee for review and discussion at the meeting on April 26, 2000.

Thank you for your prompt consideration of this request.

Correspondence concerning these questions should be directed to Sean Alan F.X. Reads, Director, Drug Regulatory Affairs, Roxane Laboratories, Inc. I can be reached by telephone at (614) 241-4131 and by telefax at (614) 276-0321. In my absence, do not hesitate to contact my colleague, Ms. Virginia Fojas, at (614) 241-4133.

Respectfully

Sean Alan F.X. Reade, M.A.
Director, Drug Regulatory Affairs
New Drugs and Regulatory Services

Chemistry Manufacturing and Controls (CMC)

1. Why is sterility assurance throughout the product shelf life required? No safety or recall issues on any existing products have been reported.

2. Delivery weight is an adequate way of conducting content uniformity for solution products and establishing bioequivalence; therefore, this should be the industry standard. The current guidelines require chemical assay.

3. Is FDA looking to add RSD requirements for delivery weights? If so, specify limits.

4. We agree that for content uniformity of suspension product, chemical assays are required. This assay can be correlated to delivery weight and we should be able to use delivery weights for priming/repriming and tail/off.

5. For excipients, FDA is requiring more testing than specked in USP/NF. Why is additional testing required to qualify the NF/USP excipeints? .

6. Why does FDA require two identification tests since HPLC is regarded as an accurate test?

7. Spray content uniformity requires 10 containers however spray content uniformity for shelf or container life is 5. The number of samples requirement should be the carne for both tests.

8. Microscopic evaluation does not mention the number of units and the acceptance criteria.

9. Foreign particle testing is required. Therefore, what methodology is used to conduct this testing on a suspension product (which is a heterogeneous system containing undissolved particles).

10. Foreign particle size can be no more than 10 microns. Methodology on how to establish this in a suspension is needed from the Agency.

11. What is the correlation between temperature cycling and sterility? We believe that sterility testing is not required.

Bioavailability and Bioequivalence: In-vitro Studies/Clinical Studies

1. The current guidelines require that for "both solution and suspension formulations of nasal sprays, the mass of drug delivered per single (unit) dose should be determined based on a stability-indicating chemical assay". This statement is appropriate when referring to a suspension, but not a solution. Delivery weights for content uniformity measurements for a solution should be acceptable since this has been well established in branded solution products currently on the market.

For suspension formulation of nasal sprays, once bioequivalence is established for content uniformity, delivery weights should be acceptable for priming/repriming and tail-off tests.

2. For BE assessment, comparative tail off profiles are requested by the Agency to ensure similarity in drug delivery as the product nears exhaustion. The Agency needs to limit the number of actuation required for the tail-off testing which should be based on the branded-labeled end of product life.

3. If the spray ***pattern of a*** nasal spray solution or suspension passes CMC requirements then why are bioequivalence requirements needed?

4. Drug particle size measurements (i.e., cascade impactor, multistage liquid impinger) should not be a criteria for showing bioequivalence especially if Industry can show alternative ways of comparing both reference and innovator products. These tests are expensive and the data is not relevant for products that are delivered to the nasal passage for local action and since the area is small.

5. In -vitro Bioequivalence requirements should NOT be required for nasal solution products with local or systemic actions.

6. In some cases the "identical actuators/pumps" are not available for development due to patent issues or because they are proprietary information. Therefore, how does the Agency expect generic companies to show bioequivalence?

7. If through due diligence it is shown that plasma concentration-time profiles cannot be established due to the fact that the drug has low to no systemic bioavailability then we should NOT be required to do a pharmacodynamic study.

8. Why does a placebo arm need to be added to an in-vivo clinical seasonal allergic rhinitis (SAR) study when the innovator product has already established efficacy and the intent is to show bioequivalence?